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In memoriam prof. dr. Ioan A. Silberg

PHOTOACTIVE BINAPHTHYL PHENOTHIAZINE DERIVATIVES

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ABSTRACT. The preparation of new *bis*-(10-alkyl-phenothiazin-3yl)-1,1'-binaphthalene derivatives 10,13, following a rational synthetic approach based on Suzuki or Negishi arylation of suitable precursors, is discussed. Positive results were obtained by Suzuki arylation of the (*RS*)-6,6'-dibromo-[1,1'-binaphthalene]-2,2'-dicarbonitrile (11) with 10-hexyl-3-(4,4,5,5-tetrametyl-1,3,2-dioxaborolan-2-yl)-phenothiazine (5) and Negishi arylation of the (*RS*)-2,2'-diidodo-[1,1'-binaphthalene] with 3-bromo-10-hexyl-phenothiazine. These compounds are candidates for new molecular materials with potentially efficient photoinduced electron transfer properties due to the axial chirality of the binaphthyl moiety combined with the low-oxidation potential and high tendency to form stable radical cations of the phenothiazine units.

INTRODUCTION

Axially chiral binaphthyl derivatives represent one of the most important groups of the artificial chiral-pool compounds [1]. Their widespread applications lay stress upon their facile accessibility in enantiomerically pure state, as well as possibility of easy structural modifications. Unique stereochemical properties of axially chiral C_2-symmetric binaphthyl moiety (symmetrically substituted at the both naphthalene rings) are the reason for enhanced interest in the synthesis, study, and application of binaphthyl derivatives.

Synthetic approaches to binaphthyl derivatives

Main synthetic approach for the synthesis of enantiomerically pure axially chiral C_2-symmetric binaphthyl derivatives consist in stereoselective formation of C-C bond connecting two naphthyl units and transformations of the groups on the binaphthalene scaffold without any configurational scrambling. Chemical transformations of the binaphthyl derivatives, except for replacing the atoms bonded directly to the binaphthyl moiety at the 2,2'-positions, do not impair the enantiomeric purity and are routinely used.

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Chiral C_2-symmetric 1,1'-binaphthyl-2,2'-disubstituted derivatives can be easily functionalized in the 3,3'-positions [2] (*via* orthometallation directed by substituents at the positions 2,2', Y = OR, NR_2) or 6,6' (by electrophilic aromatic substitution as reported for Y = OH) [3]. Substituents at the other positions (more often 4,4' and 7,7') have to be incorporated before the coupling of naphthyl units [4].

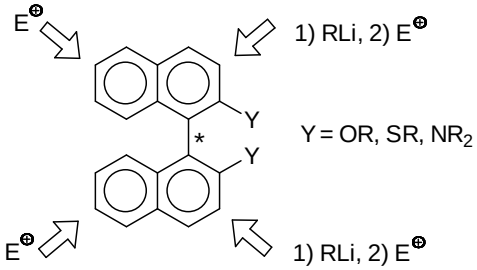


Figure 1

It is of great interest to investigate new photoactive and electroactive binaphthyl derivatives as molecular materials for potential application in optoelectronics as information storage media and logic gates (processing data). Phenothiazines derivatives as electron-rich tricyclic nitrogen-sulfur heterocycles with a low-oxidation potential and a high tendency to form stable radical cations are candidates for groups, which should bring interesting properties to binaphthyl derivatives. Besides above mentioned properties of phenothiazine derivatives, thanks to their physiological activities, pronounced biological and pharmacological activity, they were applied in a broad range as anthelmitics, antipsychotics, antiepileptics, antituberculotics and antitumor agents [5], more recently, due to their low oxidation potential and reversible oxidations, deep colored radical cation absorptions, phenothiazines have become very interesting spectroscopic probes in molecular and supramolecular arrangements for photoinduced electron transfer (PET) studies [6].

As a consequence the integration of phenothiazinyl units into conjugated chains in the sense of a "push-pull" substitution is an intriguing objective both from the synthetic and the physical properties points of view. As shown by the work of Lambert for expanded benzidines and triarylamines [7], for bridged and unbridged oligophenothiazines there is also a strong dependence of the electronic communication between aromatic units on the distance of electrophores and the nature of the bridge [8,9].

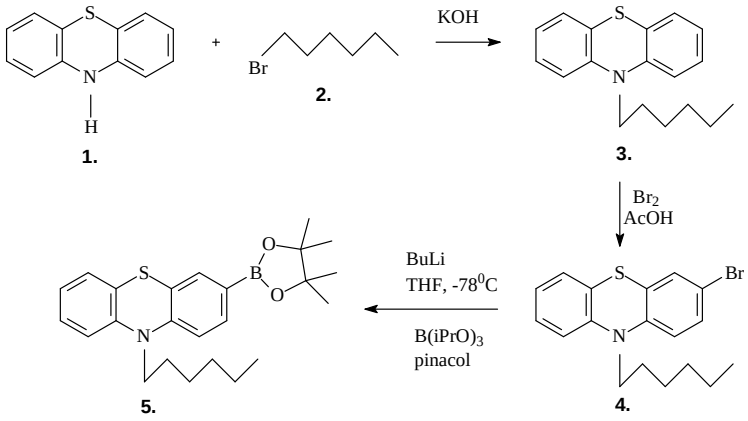
We aimed to prepare a series of binaphthyl derivatives bearing phenothiazine groups at positions 2,2' and/or 6,6'. Investigation of the photochemical and electrochemical properties of such derivatives should give

us valuable information about electronic communication among these groups *via* binaphthyl spacer as a background for construction of optoelectronic devices. In order to obtain the desired compounds **10** and **11** we proposed a rational synthetic approach based on Suzuki or Negishi arylation fo suitable binaphthyl precursors.

RESULTS AND DISCUSSIONS

For Suzuki cross-coupling approach [10] the boronic acid derivative of phenothiazine **5** was coupled with the dibromobinaphthyl derivative **10** (Scheme 3). Compounds **5** and **10** were synthesized according to the procedures described below.

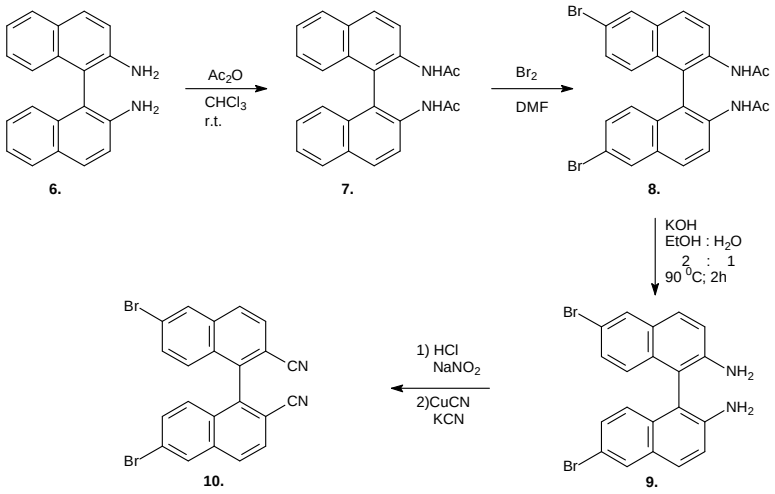
The boronic acid derivative of phenothiazine **5** was readily synthesized from alkylbromophenothiazine **4** by bromine-lithium exchange followed by quenching with trialkyl borate. The derivative **4** was previously synthesized from the *N*-hexylphenotiazine **10** by bromination reaction with bromine in acetic acid. (Scheme 1)



Scheme 1

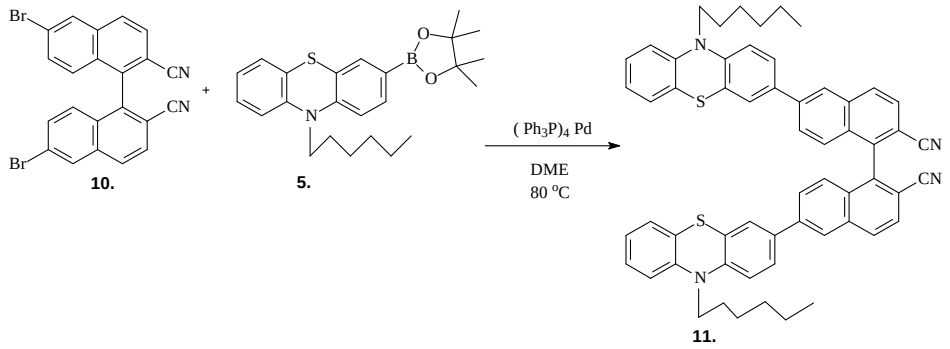
The synthesis of dibromo-dicyanobinaphthyl **10** started with 2,2'-diaminobinaphthyl **6** which was acetylated with acetic anhydride and the protected compound **7** was brominated to give the 6,6'-dibromobinaphthyl derivative **8**. This intermediate was deprotected and then converted into the corresponding dicyanodibromobinaphthyl derivative **10** by diazotization followed by Sandmeyer substitution reaction with KCN and CuCN (Scheme 2). The hydrolysis of the cyano groups in presence of NaOH in diethylene glycol was attempted, but unfortunately it was not successful.

Suzuki coupling of phenothiazine-boronic acid **5** with dibromobinaphthyl **10** under standard conditions in DME / water at 80 ℃ with $Pd(PPh_3)_4$ for 3 days gave the target compound **11** as a brown precipitate in good yield (Scheme 3). The structure of compound **11** was assigned by ^{1}H-NMR and ^{13}C-NMR.



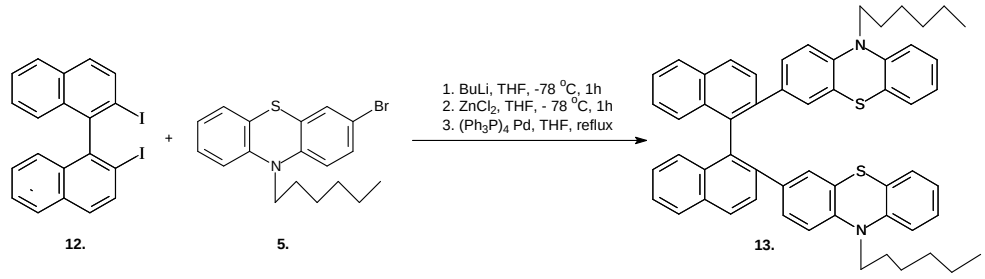
Scheme 2

The hydrolysis of the nitrile functional groups of **11** and the reduction of the intermediate carboxylic acid to hydroxymethyl derivatives were attempted, but unsatisfactory results were obtained, most probably because of steric reasons.



Scheme 3

Negishi arylation also offer a broadly applicable methodology for biaryl synthesis with a relatively high functional group tolerance. The target compound **13** was obtained by Negishi reaction of 2,2'-diiodo-binaphthyl **12** with phenothiazinylzinc halides (Scheme 4). The purification of compounds by column chromatography was very difficult because of very close R_f values of **13** and 10-hexyl phenothiazine dimer formed as side product of this homocoupling reaction.



12. **5.** **13.**

Scheme 4

CONCLUSIONS

New *bis*-(10-alkyl-phenothiazin-3yl)-1,1'-binaphthalene derivatives **10**, **13** were synthesized by Suzuki or Negishi coupling reactions of properly substituted phenothiazine and binapthyl derivatives. Strategies for the syntheses of starting compounds were also developed.

EXPERIMENTAL PART

All reaction were carried out in flame-dried Schlenk flasks under nitrogen by using septum and syringe techniques. Reagents, catalysts, ligands and solvents were purchased reagent grade and used without further purification. Solvents were dried and distilled. Column cromatograpfy: silica gel 30–60 µm and thin-layer chromatography (TLC) on Silufol UV 254 foils: silica gel plates. Melting points were measured on a Koffler block and are uncorrected values. ^{1}H and ^{13}C NMR spectra were measured on a Varian Gemini 300 (300 MHz) instrument in $CDCl_3$ and DMSO with tetramethylsilane as internal standard.

10-hexylphenothiazine (3)

3 was prepared according to [11] by a modified procedure.

A mixture of phenothiazine (2 g, 0.01 mol) and powdered KOH (1.03 g, 0.02 mol) in dry DMF (10 mL) was stirred under N_2 for 30 min . The 1-bromohexane (5.8 mL) was introduced and the mixture was stirred 48 h at r.t. The mixture was poured into water (50 mL) and extracted with hexane. After the removal of the solvent 2.46g of the pure product (η = 86%) remained. Spectral analyses were in good agreement with [11].

3-Bromo-10-hexylphenothiazine (4) [12]
Sodium hydroxide (0.62g, 0.0155 mol) was dissolved in 38 mL acetic acid under N_2. 10-hexylphenothiazine (1.5g, 0.0053 mol) solution in $CHCl_3$ (10 mL) was added. The solution was cooled to 0-5 ºC on ice–bath. Bromine (0.3 mL, 0.005 mol) dissolved in acetic acid (5 mL) was added drop wise. The suspension was stirred at r.t. for 1 h. Acetic acid was removed under reduced pressure, giving a purple solid residue. The residue was dissolved in a mixture of saturated aqueous sodium bicarbonate solution (100 mL) and CH_2Cl_2 (100 mL). The aqueous phase was separated from the organic phase and extracted with CH_2Cl_2 (100 mL). The combined organic layer were dried over Na_2SO_4 and filtered chromatography on silica gel with hexane as eluent. 1,5 g of product was obtained. (η = 90%). Spectral analyses were in good agreement with [12]
10-Hexyl-3-(4,4,5,5-tetrametyl-1,3,2-dioxaborolan-2-yl)-10*H*-phenothiazine (5) [13]
To a solution of **4** in anhydrous THF (40 mL) under N_2 were added drop wise at –78 ºC a 2.5 M solution of BuLi in hexane (9 mL). This yellow viscous mixture was stirred at –78 ºC for 15 min. Before triisopropyl borate was added drop wise and stirring was continued for another 30 min at –78 ºC. Then, the cooling bath was removed and the mixture was allowed to warm up to r.t. and the stirring was continued for another 1 h. To the yellow reaction mixture was added a solution of dry pinacol (1.7g, 0.015 mol) in anhydrous THF (10 mL) and the stirring was continued for 48 h to give an orange mixture. After the addition of AcOH (0.5 mL, 0.007 mol) the mixture turns light orange and highly viscous. After stirring for 16 h, aq. sat. Na_2SO_3 solution (100 mL) was added to the mixture and the aqueous layer was extracted with Et_2O (4 x 100 mL). The combined organic phases were dried ($MgSO_4$) and the solvents were removed in vacuum. The residue was purified by column chromatography on silica gel (hexanes) to furnish 0.76 g (30 %) as orange colored oil.
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.87ppm (t, 3H), 1.30 ppm (m, 16 H), 1.43 ppm (m, 2H), 1.79 ppm (m, 2H), 3.84 ppm (t, 2H), 6.88 ppm (m, 3H), 7.11 ppm (m, 2H), 7.58-7.61 ppm (m, 2H).
(*RS*)-*N,N'*- (1,1'-binaphthalene-2,2'diyl)-diacetamide (7)
Mixture of 2,2'-diamino-binaphthyl (5 g, 18 mmol) and acetic anhydride (6.7, 71 mmol) was stirred at room temperature for 2h to give pure compound (**7**)(η = 100 %).
(*RS*)-*N,N'*- (6,6'-dibromo-1,1'-binaphthalene-2,2'-diyl)-diacetamide (8)
The flask containing compound **7** (0.73 g, 2 mmol), bromine (0.52 mL, 0.01 mmol) and anhydrous DMF (15 mL) was flushed with N_2 atmosphere. The reaction mixture was stirred and heated on the oil bath at 90 ºC for 11 h. The resulting mixture was washed with water, 10 % aqueous NaOH (10 mL) and was extracted with 50 mL $CHCl_3$, dried over anhydrous Na_2SO_4. Solvent was evaporated and the product made complex with DMF. The mixture was dissolved in minimum amount of CH_2Cl_2 and hexanes, after the precipitate was filtered. (η = 95 %). Crude product was used in following reaction step.
(*RS*)-6,6'-Dibromo-1,1'-binaphthalene-2,2'-diamine (9)
The flask containing compound **8** (1.043 g, 2 mmol), KOH (4.44 g, 79 mmol) and solution of EtOH : H_2O = 2 : 1 (40 mL) was stirred and heated on the oil bath at 90 ºC under N_2 for 2 h. The reaction mixture was quenched with 50 mL $CHCl_3$ and was washed with NH_4Cl. The crude product 0.69 g. (η = 80 %) was used in following reaction step without further purification.

(*R,S*)6,6'-Dibromo-1,1'-binaphthalene-2,2'-dicarbonitrile (10)

A solution of diamine **9** (0.69 g, 1.5 mmol) in 27 % HCl (10 mL) was diazotized by addition of solid $NaNO_2$ (0.45 g, 6.5 mmol) at 0 ºC. The mixture was stirred and the temperature was maintained at 0–5 ºC for 2 h. The filtered diazo-solution was added to the mixture of KCN and CuCN (0.23 g CuCN in 5.6 mL of 5 % KCN solution). The reaction mixture was warmed on the water-bath at 80 ºC for 15 min. and the solid filtered off and washed with dilute HCl (10 mL) and water (100 mL). After drying, the product was obtained in 95 % yield.

^{1}H NMR (DMSO, 300 MHz) ppm: δ = 6.99 ppm (d, 2H), 7.54 ppm (d, 2H), 7.86 ppm (d, 2H), 8.18 ppm (d, 2H), 8.43 ppm (s, 2H)

^{13}C NMR (DMSO, 300 MHz): δ ppm = 119.9 (CN), 126.4 (CH), 128.3 (CH), 129.9 (CH), 130.5(CH), 130.5 (CH), 130.9 (CH), 130.9 (CH), 131.7 (CH), 131.9 (CH), 131.6 (CH), 131. 8(CH)

(*R,S*)6,6'-Bis-(N-hexylphenothiazin-3-yl)-1,1'-binaphthalene-2,2'-dicarbonitrile (11)

To the mixture of **10** (0.5g, 0.001 mol) and **5** in degassed 1,2-dimetoxyethane (60 mL) were added K_2CO_3 (0.1 g, 0.0008 mol) dissolved in a minimum amount of water, and $(Ph_3P)_4Pd$ (0.0008 g, 16 µmol). The reaction mixture was heated to reflux for 3 days under N_2. After the cooling to r.t. H_2O (300 mL) was added and the precipitate was collected by suction filtration and dried in vacuum. The residue was purified by column chromatography on silica gel ($CHCl_3$) to give 0.1 g (72 %) after recrystallization from methanol.

^{1}H NMR (DMSO, 300 MHz) ppm: δ = 0.87 ppm (t, 6H), 1.29 ppm (m, 12 H), 1.67 ppm (m, 4H), 3.80 ppm (t, 4H), 6.80-7.22 ppm (m, 12H), 7.60 ppm (m, 6H), 7.84 ppm (d, 2H), 8.17 ppm (dd, 3H), 8.42 ppm (dd, 3H)

^{13}C NMR (DMSO, 300 MHz): δ ppm = 13.8 (CH_3), 21.9 (CH_2), 25.9 (CH_2), 30.8 (CH_2), 199. 9 (CN), 126.9 (CH), 128.3 (CH), 128.8 (CH), 129.94 (CH), 130.5 (CH), 130.9 (CH), 131.1 (CH), 131.4 (CH), 131.5 (CH), 131.7 (CH), 131.9 (CH), 133.1 (CH)

(*R,S*) 2,2' –Bis (N-hexylphenothiazin-3-yl) 1,1'-binaphthalene (13)

To a solution of **4** (468 mg, 1.34 mmol) in dry THF (10 mL) under N_2 were added drop wise at –78 ºC a 2.5 M sol BuLi (6 mL). This yellow viscous mixture was stirred at –78 ºC for 1h before zinc chloride (222 mg, 1.6 mmol) and THF (2 mL) was added drop wise and stirring was continued for another 1h at –78 ºC. Then the cooling bath was removed and the mixture was allowed to warm up to r.t. The mixture of **12** (116 mg, 0.2 mmol), $(Ph_3P)_4Pd$ (0.0006 g, 11 µmol) in dry THF (6 mL) was added drop-wise to the yellow reaction mixture and the mixture was refluxed for 1 h to give a brown mixture. After 1 hour, the reaction mixture was cooled down to r.t and diluted HCl (10 mL) was added; the aqueous layer was extracted with Et_2O (4 x 100mL). The combined organic phases were dried ($MgSO_4$) and the solvents were removed in vacuum. The residue was recrystallized in methanol to furnish 50 mg (27 %) as white precipitate.

^{1}H NMR (DMSO, 300 MHz): δ = 0.87 ppm (t, 6H), 1.29 ppm (m, 12 H), 1.67 ppm (m, 4H), 3.80 ppm (t, 4H), 6.80-7.25 ppm (m, 17H), 7.45 ppm (t, 2H), 7.50 ppm (dd, 3H), 7.70 ppm (t, 2H), 8.05 ppm (dd, 3H).

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